Prediagnostic Human T Lymphotropic Virus Type I Provirus Loads Were Highest in Jamaican Children Who Developed Seborrheic Dermatitis and Severe Anemia

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In a recent clinical analysis of 308 Jamaican children, human T lymphotropic virus type I (HTLV-I) infection was found to be associated with significantly higher incidence rates of seborrheic dermatitis, eczema, and persistent hyperreflexia of the lower limbs and with nonsignificantly increased rates of severe anemia and abnormal lymphocytes. Results of examination of HTLV-I viral markers in the 28 HTLV-I–infected children provided virologic support for the epidemiologic associations of HTLV-I with seborrheic dermatitis and severe anemia in childhood.

Human T lymphotropic virus type I (HTLV-I) is associated with adult T cell leukemia/lymphoma (ATL) and a neurologic disease called "HTLV-I–associated myelopathy/tropical spastic paraparesis" (HAM/TSP) [1–3]. Both diseases are associated with elevated HTLV-I provirus loads and antibody titers, which suggests the importance of viral markers as surrogates of pathogenesis [4–6].

Patients with ATL have been described as having a T helper cell type 2 cytokine pattern, which promotes down-regulation of the cell-mediated immune response [7]. In contrast, patients with HAM/TSP have been described as having a T helper cell type 1 cytokine pattern, which supports a cell-mediated immune response [7, 8]. HLA class II alleles associated with ATL in the Jamaican population include DRB1*1501, DRB1*1101, and DQB1*0602 [9].

HTLV-I infection in early childhood is believed to be an important risk factor for the development of ATL. Among children, HTLV-I is associated with infective dermatitis (ID) [10]. A patient with ID was found to have prediagnostic provirus loads and antibody titers similar to those reported for adults with HAM/TSP [11]. We detected, among a cohort of Jamaican children, several additional HTLV-I–associated conditions, including seborrheic dermatitis, eczema, persistent hyperreflexia, and severe anemia, in addition to findings of "abnormal lymphocytes" (i.e., the number of lymphocytes with abnormal morphology per 100 peripheral blood mononuclear cells [PBMCs] [12]). The present study examines the prediagnostic levels of viral, immunologic, and genetic markers among the 28 HTLV-I–infected children from the cohort, to determine whether these markers are associated with the development of health outcomes.

Subjects, materials, and methods. The study included 28 HTLV-I–infected children who were born to 212 HTLV-I–seropositive women who enrolled in a prospective study of mother-to-infant transmission of HTLV-I from January 1989 through August 1990 in Kingston, Jamaica [13]. Informed consent was obtained from the parents of the study participants, and human-experimentation guidelines of the US Department of Health and Human Services and the University of the West Indies (Kingston, Jamaica) were followed in the conduct of clinical research.

The children were breast-fed for a mean of 17 months, became infected with HTLV-I at an estimated mean age of 14 months, and were followed clinically for a mean of 6.7 years. The children had a physical examination and phlebotomy performed every 6 weeks for the first 3 months of life, every 3 months up to 2 years of age, and every 6 months thereafter (up to a maximum of 10 years of age).

A pediatrician who was blinded to the HTLV-I–infection status of the children performed a general physical examination

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and phlebotomy at every clinic visit and also performed a skin assessment and a neurologic screening examination at visits occurring from age 2.5 years to 10 years. Seborrheic dermatitis was diagnosed if a child had clinical signs of the condition at $\geqslant$1 clinic visit, including the presence of greasy, red, scaly, usually nonpruritic eruptions, which were predominantly located in hair-bearing and intertriginous areas. Eczema was diagnosed if a child had clinical signs of the condition at $\geqslant$3 clinic visits. Infantile eczema appeared as an intensely pruritic rash of nonflexural surfaces and of the dorsum of the hands, limbs, and chest of infants and children who were 1 month to 3 years of age. Childhood eczema occurred among children 4–10 years of age; it appeared as a dry, papular, and intensely pruritic rash involving scaly patches that were distributed on the wrists, the ankles, the antecubital and popliteal fossae extensor surfaces of the limbs, and the palmer and plantar surfaces of the hands and feet. Persistent hyperreflexia of the lower limbs was diagnosed if a child received, at a minimum of 2 clinic visits, a score of 4+ during an examination of reflexes (scale, 1–5; a score of 1 denoted areflexia, 2 denoted hyporeflexia, 3 denoted normal reflexes, 4 denoted hyperreflexia, and 5 denoted clonus).

Blood samples obtained at clinic visits that occurred when children were 30–120 months of age were collected in an EDTA tube for determination of the complete blood count and the differential count; the samples were tested using standard methods. "Severe anemia" was defined by hemoglobin (Hgb) levels less than the age-specific limits of the normal distribution (i.e., an Hgb level <9.0 g/dL for children 30–36 months of age, an Hgb level <9.6 g/dL for children 37–66 months of age, and an Hgb level <10.0 g/dL for children 67–120 months of age). The hematologist's notes were used to determine whether anemia was normochromic, normocytic or hypochromic, microcytic. Abnormal lymphocytes were counted by a hematologist during microscopic review of peripheral blood smears. Analysis of abnormal lymphocytes included adjustment for the white blood cell count and was limited to the presence of abnormal lymphocytes at a frequency of $\geqslant$3.0% of PBMCs.

A nurse obtained information on maternal income and duration of breast-feeding from each child's mother. Maternal income (all dollar amounts are given in Jamaican dollars) was stratified as low (<\$100/week), medium (\$100–\$200/week), or high (>\$200/week). Duration of breast-feeding was defined as the period between the child's birth and the midpoint between the last clinic visit at which the mother reported breast-feeding and the first clinic visit at which she reported having stopped breast-feeding.

The child's age at HTLV-I infection was based on polymerase chain reaction (PCR) analysis of lymphocyte specimens that were obtained at the child's estimated age at seroconversion, which previously was determined by Western blot analysis of serial samples obtained, from birth up to 24 months of age, from children who were found to be seropositive by ELISA performed from 12 to 24 months of age [13]. The child's age at infection was estimated to be the midpoint between the date that the first sample with a positive PCR result was obtained and the date that the last sample with a negative PCR result was obtained.

Analysis of all markers involved the use of specimens obtained ~12 months after the child's estimated age at infection. HTLV-I provirus DNA load was measured in triplicate by use of the ABI PRISM 7700 Sequence Detector [5]. HTLV-I antibody titer was analyzed using the Vironostika HTLV-I/II Microelisa System (Organon Teknika). The endpoint dilution was reported for each child, on the basis of 5-fold dilutions of each child's sample. HTLV-I Tax-specific antibody was measured by ELISA (Tsukuba Research Laboratories, Eisai) [14].

Cytokines were analyzed in serum samples by use of commercial assays (R&D Systems). The lower limits of detection were as follows: for interferon (IFN)–γ, 10 pg/mL; for tumor necrosis factor (TNF)–α, 1 pg/mL; for interleukin (IL)–1α, 1 pg/mL; for IL-4, 3 pg/mL; for IL-6, 0.7 pg/mL; and for IL-10, 3 pg/mL. HLA class II molecular typing was done by single-strand conformation polymorphism analysis in combination with PCR sequence-specific primers [15].

The Wilcoxon rank sum test was used to compare the geometric means of provirus loads and antibody titers of children grouped according to health-outcome status, sex, and the child's age at infection (dichotomized at median age). The Fisher's exact test was used to compare the frequencies of Tax-specific antibody of children grouped by health-outcome status and levels of proviral load and titer (dichotomized at median values); the Fisher's exact test was also used to compare frequencies of HLA class II alleles, as well as cytokine levels >30 pg/mL among children, according to health-outcome status. Spearman's rank correlation coefficient was used to measure the association of provirus load and antibody titer.

P values were derived from 1- or 2-tailed tests. In the analysis of HTLV-I provirus load and antibody titer, *P* values were derived from 1-tailed tests based on a priori hypotheses that children with health outcomes of interest would have higher geometric mean levels of these viral markers, compared with children without specific health outcomes. For all other analyses, *P* values were derived from 2-tailed tests. All statistical analyses were conducted using Statistical Analysis Software (version 6.03; SAS Institute).

Results. The cohort of 28 HTLV-I–infected children included 16 males (57.1%) and 12 females (42.9%). The majority of children (79%) were born to women in the lower or middle income categories. The geometric mean of the HTLV-I provirus loads of the children was 3.7 copies/100 PBMCs (95% confidence interval [CI], 2.4–5.9 copies/100 PBMCs) (table 1).

Table 1. Human T lymphotropic virus type I (HTLV-I) viral markers and cytokine levels in 28 HTLV-I–infected Jamaican children.

Subject	Age at infection, months	Provirus DNA load, no. of copies/ 100 PBMCs	Antibody titer	Anti-Tax antibody	Cytokine level, pg/mL					
					IFN-γ	TNF-α	IL-1α	IL-4	IL-6	IL-10
1	9.9	4.4	62,797	+	UD	UD	UD	UD	UD	UD
2	14.1	9.7	21,675	+	UD	UD	UD	UD	UD	UD
3	6.9	3.6	6217	−	UD	UD	0.1	UD	743	UD
4	26.7	13.3	5293	+	UD	3027	134	UD	424	31
5	21.2	3.7	375,116	+	UD	UD	UD	UD	UD	UD
6	8.3	5.1	4837	+	UD	UD	UD	UD	UD	UD
7	17.3	2.9	12,183	+	UD	UD	UD	UD	UD	UD
8	12.8	8.0	390,625	+	UD	UD	UD	UD	UD	UD
9	21.1	6.7	47,376	+	UD	UD	UD	UD	UD	UD
10	8.5	16.1	31,404	+	UD	UD	UD	UD	UD	UD
11	9.2	0.7	274	−	UD	UD	UD	UD	UD	UD
12	15.9	15.3	390,625	+	UD	UD	UD	UD	UD	UD
13	21.9	1.39	680	−	UD	UD	UD	UD	UD	UD
14	7.6	2.5	1157	+	UD	UD	UD	UD	UD	UD
15	10.2	6.7	18,205	+	UD	UD	UD	UD	UD	UD
16	9.7	7.1	390,625	+	UD	2345	15	UD	20477	UD
17	3.7	1.5	266	−	UD	1088	30	UD	15507	UD
18	13.3	0.4	3482	−	UD	UD	UD	UD	UD	UD
19	12.0	1.8	1961	−	UD	570	46	UD	14921	13
20	14.9	4.7	6733	+	UD	UD	UD	UD	UD	UD
21	17.6	14.8	45,688	+	21	UD	UD	UD	UD	UD
22	7.1	1.9	22,086	+	UD	UD	UD	UD	UD	UD
23	12.0	0.1	706	−	UD	UD	UD	UD	UD	UD
24	21.2	12.9	14,805	+	UD	1649	134	UD	UD	186
25	12.4	8.6	5216	+	UD	UD	UD	UD	UD	UD
26	18.3	3.2	17,265	+	UD	UD	UD	UD	4.1	UD
27	25.2	0.5	7647	+	26	UD	UD	UD	UD	UD
28	7.9	15.3	17,172	+	UD	UD	UD	UD	510	UD

NOTE. IFN, interferon; IL, interleukin; PBMCs, peripheral blood mononuclear cells; TNF, tumor necrosis factor; UD, undetectable; +, present; −, absent.

HTLV-I provirus loads did not vary significantly by either the child's age at infection or sex ($P = .97$ and $P = .16$, respectively; data not shown). Children's HTLV-I antibody titers at this same point in time had a geometric mean of 11,515 (95% CI, 5357–27,748) and were significantly correlated with provirus load ($r = 0.57$; $P = .002$). Seventy-five percent of the infected children had Tax-specific antibody, including all children with "high" (greater than the median value) provirus loads or antibody titers ($P = .0006$, for each) (table 2).

Seven HTLV-I–infected children developed seborrheic dermatitis at a mean age of 4.9 years. Children who developed seborrheic dermatitis had a higher mean provirus load than did children without seborrheic dermatitis ($P = .07$, by 1-tailed test) (table 2). This association was unaffected by adjustment for maternal income.

Four of the 28 infected children had severe anemia diagnosed at a mean age of 2.5 years. Anemia was characterized as hypochromic, microcytic, which is consistent with iron deficiency. Children with anemia had a significantly higher mean provirus load than did children without this condition ($P = .04$, by 1-tailed test). After adjustment for maternal income, this association was of marginal statistical significance ($P = .06$, by 1-tailed test). Three of the 4 children with anemia also had seborrheic dermatitis diagnosed. These 3 children had provirus loads of 13.3–16.1 copies/100 PBMCs. For 2 of these 3 children, the diagnosis of anemia preceded the diagnosis of seborrheic dermatitis.

The frequency of abnormal lymphocytes among 4 HTLV-I–infected children (mean age, 6.7 years) was $\geqslant$3.0%. Children with this frequency of abnormal lymphocytes had a lower mean

Table 2. Distribution of viral markers in human T lymphotropic virus type I (HTLV-I)–infected Jamaican children, according to health outcomes.

Health outcome[a]	No. of children	Mean no. of provirus copies/ 100 PBMCs (95% CI)	P^b	Mean antibody titer[c] (95% CI)	P^d	Proportion with Tax-specific antibody, %	P^e
Seborrheic dermatitis			.07		.10		.28
Yes	7	7.5 (4.3–13.0)		29.3 (10.6–81.2)		100.0	
No	19	3.1 (1.7–5.7)		10.9 (4.2–28.2)		73.7	
Eczema			.13		.23		1.00
Yes	8	5.9 (2.9–11.8)		19.3 (4.5–83.7)		87.5	
No	18	3.3 (1.7–6.1)		14.0 (5.5–35.7)		77.8	
Hyperreflexia			.49		.35		1.00
Yes	9	4.1 (1.8–9.1)		18.9 (4.1–87.7)		77.8	
No	17	3.9 (2.1–7.2)		12.2 (5.2–28.8)		82.4	
Anemia			.04		.46		.55
Yes	4	9.6 (4.0–22.7)		16.5 (1.4–192.3)		100.0	
No	22	3.4 (2.7–5.7)		13.9 (6.2–31.0)		77.3	
⩾3.0% Abnormal lymphocytes[f]			.04		.21		.15
Yes	4	1.1 (0.1–8.3)		7.0 (1.1–44.5)		60.0	
No	22	4.9 (3.3–7.4)		16.2 (7.0–37.3)		86.4	

NOTE. CI, confidence interval; PBMCs, peripheral blood mononuclear cells.

[a] Assessed from age of 2.5 years to age of 10 years, when there were 26 HTLV-I–infected children in clinical follow-up.

[b] *P* values for the comparison of mean provirus loads by diagnosis category were derived from 1-tailed tests.

[c] Titer is the value shown multiplied by 1000.

[d] *P* values for the comparison of mean antibody titers by diagnosis category were derived from 1-tailed tests.

[e] *P* values for the comparison of proportions of Tax-specific antibody were derived from 2-tailed tests.

[f] "Abnormal lymphocytes" were defined as the no. of lymphocytes with abnormal morphology per 100 PBMCs.

provirus load than did children without this frequency of abnormal lymphocytes ($P = .04$, by 1-tailed test). The abnormal lymphocytes detected among these children were not described as "flower cells," which are characterized by polylobulated nuclei and are commonly found in patients with ATL.

Children with or without the targeted health outcomes had similar mean HTLV-I antibody titers and frequencies of Tax-specific antibody (table 2). Allele frequencies of DRB1*1501, DRB1*1101, and DQB1*0602 did not vary significantly according to health-outcome status (data not shown). Elevated levels of cytokines were not associated with any of the health outcomes studied.

Discussion. HTLV-I infection is known to be associated with ID in childhood [10]. The only child with ID in our cohort had a provirus load similar to the provirus loads reported for adult patients with HAM/TSP [11]. The current analysis of HTLV-1–infected children from the cohort revealed that children who developed seborrheic dermatitis had a higher mean HTLV-I provirus load, compared with children who did not develop seborrheic dermatitis, although this finding was of marginal statistical significance. These data may suggest a role for HTLV-I provirus load in the pathogenesis of seborrheic dermatitis, a mild inflammatory dermatitis associated with increased colonization by *Pityrosporum ovale,* which is a lipophilic yeast that occurs naturally on the human skin [16]. Severe seborrheic dermatitis has been documented in human immunodeficiency virus (HIV)–infected children 2–5 years of age [17]. Development of this skin condition in HIV-infected children raises the possibility of immune suppression as a factor in the development of seborrheic dermatitis. The high prediagnostic HTLV-I provirus load and the subsequent colonization of *P. ovale* could be indicators of failure of the immune system to control viral and fungal pathogens, resulting in the development of seborrheic dermatitis in HTLV-I–infected children.

The association of severe, hypochromic/microcytic anemia with an elevated provirus load was mitigated by adjustment for maternal income, indicating that a correlate of socioeconomic status partially accounts for this association. Iron-deficiency anemia may be due to parasitic infection or poor nutrition, which are indicators of low socioeconomic status. The HTLV-I provirus loads of 3 children who had anemia and seborrheic dermatitis were 3 of the 4 highest levels noted in the present study and were similar to levels reported for patients with HAM/TSP [5]. Children with both seborrheic dermatitis and anemia may be a subset of children with more-severe immune suppression who may be at higher risk for more-serious HTLV-I–associated diseases.

The marginal association of abnormal lymphocytes with low

HTLV-I provirus loads did not support our a priori hypothesis and is inconsistent with findings from studies of adults. Abnormal lymphocytes with flower cell features are a characteristic feature of ATL [1]. However, none of the infected children in the present study had flower cells. It is possible that differences in the definition of abnormal lymphocytes and in the methods of measurement account for these inconsistent results.

None of the health outcomes studied in the present analysis were associated with the cytokines or the HLA alleles that were measured. The lack of associations could be the result of the low power of this study. A study with a larger sample size is needed to further investigate these associations.

In summary, a high prediagnostic HTLV-I provirus load measured ~12 months after infection was marginally associated with the development of seborrheic dermatitis an average of 31 months later. HTLV-I provirus load was highest among 3 children who developed both seborrheic dermatitis and severe anemia. These data suggest that HTLV-I may be associated with a broader range of morbidity among children, including seborrheic dermatitis. In addition, further study of the role of anemia in the pathogenesis of HTLV-I–associated diseases is warranted.

The present data should be interpreted with caution. There was considerable overlap in the health outcomes of these children, which made it difficult to discern the relationship of any one outcome to a viral marker.

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